

IT IS CLAIMED:

1. An antibacterial compound consisting of a substantially uncharged antisense oligomer containing from 8 to 40 nucleotide subunits, said oligomer including a targeting nucleic acid sequence at least 10 nucleotides in length which is effective to hybridize to (i) a bacterial tRNA sequence or (ii) a target sequence, containing a translational start codon, within a bacterial nucleic acid which encodes a protein associated with cell division or the cell cycle,

said protein being selected from the group consisting of *zipA*, *sulA*, *secA*, *dicA*, *dicB*, *dicC*, *dicF*, *ftsA*, *ftsI*, *ftsN*, *ftsK*, *ftsL*, *ftsQ*, *ftsW*, *ftsZ*, *murC*, *murD*, *murE*, *murF*, *murG*, *minC*, *minD*, *minE*, *mraY*, *mraW*, *mraZ*, *seqA*, and *ddlB* proteins, carbamate kinase, D-ala D-ala ligase, topoisomerase, alkyl hydroperoxide reductase, thioredoxin reductase, dihydrofolate reductase, and cell wall enzyme;

wherein: each of said subunits comprises a 5- or 6-membered ring supporting a base-pairing moiety effective to bind by Watson-Crick base pairing to a respective nucleotide base in the bacterial nucleic acid sequence,

adjacent subunits are joined by uncharged linkages selected from the group consisting of: uncharged phosphoramidate, phosphorodiamidate, carbonate, carbamate, amide, phosphotriester, alkyl phosphonate, siloxane, sulfone, sulfonamide, sulfamate, thioformacetyl, and methylene-N-methylhydroxylamino, or by charged linkages selected from the group consisting of phosphate, charged phosphoramidate and phosphorothioate,

and the ratio of uncharged linkages to charged linkages in the oligomer is at least 4:1.

2. The compound of claim 1, wherein the targeting nucleic acid sequence is complementary to a target sequence containing a translational start codon.

3. The compound of claim 1, wherein the oligomer is a morpholino oligomer.

4. The compound of claim 3, wherein each uncharged linkage is a phosphorodiamidate linkage as represented at Figure 2B, where $X=NR_2$, where R is hydrogen or methyl, $Y=O$, and $Z=O$.

5. The compound of claim 3, wherein each linkage is a phosphorodiamidate linkage as represented at Figure 2B, where $X=NR_2$, where R is hydrogen or methyl, $Y=O$, and $Z=O$.

6. The compound of claim 1, wherein the antisense oligomer has a length of from 15 to 20 subunits.

7. The compound of claim 2, wherein the target sequence is a translation initiation region in an mRNA transcribed from a bacterial gene selected from the group consisting of *zipA*, *sulA*, *secA*, *dicA*, *dicB*, *dicC*, *dicF*, *ftsA*, *ftsI*, *ftsN*, *ftsK*, *ftsL*, *ftsQ*, *ftsW*, *ftsZ*, *murC*, *murD*, *murE*, *murF*, *murG*, *minC*, *minD*, *minE*, *mraX*, *mraW*, *mraZ*, *seqA* and *ddlB*.

8. The compound of claim 7, wherein the target sequence is a translation initiation region in an mRNA transcribed from a *dic* gene selected from the group consisting of *dicA*, *dicB*, *dicC* and *dicF*.

9. The compound of claim 8, wherein the targeting sequence has a sequence selected from the group consisting of SEQ ID NO:45 (*E. coli dicF*), SEQ ID NO:48 (*E. coli dicA*), SEQ ID NO:49 (*E. coli dicB*), SEQ ID NO:50 (*E. coli dicC*); and SEQ ID NO:61 (*S. typhi. dicA*).

10. The compound of claim 9, wherein the targeting sequence has the sequence presented as SEQ ID NO:45 (*E. coli dicF*).

11. The compound of claim 10, wherein the antisense oligomer is a morpholino oligomer.

12. The compound of claim 2, wherein the targeting sequence is complementary to a translation initiation region in an mRNA transcribed from a *secA* gene, and has a sequence selected from the group consisting of SEQ ID NO:47 (*E. coli secA*), SEQ ID NO:67 (*Staph. aureus secA*), SEQ ID NO:79 (*H. pylori secA*), and SEQ ID NO:91 (*Treponema pallidum secA*).

13. The compound of claim 12, wherein the targeting sequence has the sequence presented as SEQ ID NO: 47 (*E. coli secA*).

14. The compound of claim 13, wherein the oligomer is a morpholino oligomer.

15. The compound of claim 2, wherein the targeting sequence has a sequence selected from the group consisting of SEQ ID NO: 103 (*E. faecium* carbamate kinase); SEQ ID NO: 104 (*E. faecium* D-ala D-ala ligase); SEQ ID NO: 105 (*E. faecalis* topoisomerase); SEQ ID NO: 107 (*E. faecalis repA*); SEQ ID NO: 108 (*E. faecalis* alkyl hydrogen peroxide reductase); SEQ ID NO: 109 (*E. faecalis* thioredoxin reductase); SEQ ID NO: 110 (*E. faecalis* dihydrofolate reductase); SEQ ID NO: 111 (*E. faecalis ftsA*); and SEQ ID NO: 112 (*E. faecalis* cell wall enzyme).

16. The compound of claim 15, wherein the oligomer is a morpholino oligomer.

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B4 17. A method of treating a bacterial infection in a human or mammalian animal subject, comprising

administering to the subject, in a pharmaceutically effective amount, a substantially uncharged antisense oligomer containing from 8 to 40 nucleotide subunits, including a targeting nucleic acid sequence at least 10 nucleotides in length which is effective to hybridize to (i) a bacterial tRNA or (ii) a target sequence, containing a translational start codon, within a bacterial nucleic acid which encodes a protein associated with cell division or the cell cycle,

said protein being selected from the group consisting of *zipA*, *sulA*, *secA*, *dicA*, *dicB*, *dicC*, *dicF*, *ftsA*, *ftsI*, *ftsN*, *ftsK*, *ftsL*, *ftsQ*, *ftsW*, *ftsZ*, *murC*, *murD*, *murE*, *murF*, *murG*, *minC*, *minD*, *minE*, *mraY*, *mraW*, *mraZ*, *seqA*, and *ddlB* proteins, carbamate kinase, D-ala D-ala ligase, topoisomerase, alkyl hydroperoxide reductase, thioredoxin reductase, dihydrofolate reductase, and cell wall enzyme;

wherein: each of said subunits comprises a 5- or 6-membered ring supporting a base-pairing moiety effective to bind by Watson-Crick base pairing to a respective nucleotide base in the bacterial nucleic acid sequence,

adjacent subunits are joined by uncharged linkages selected from the group consisting of: uncharged phosphoramidate, phosphorodiamidate, carbonate, carbamate, amide, phosphotriester, alkyl phosphonate, siloxane, sulfone, sulfonamide, sulfamate, thioformacetyl, and methylene-N-methylhydroxylamino, or by charged linkages selected from the group consisting of phosphate, charged phosphoramidate and phosphorothioate,

and the ratio of uncharged linkages to charged linkages in the oligomer is at least 4:1.

18. The method of claim 17, wherein the targeting nucleic acid sequence is complementary to a target sequence containing a translational start codon.

19. The method of claim 17, wherein the oligomer is a morpholino oligomer.

20. The method of claim 19, wherein the uncharged linkages are selected from the group consisting of the structures presented in Figures 2A through 2D.

21. The method of claim 19, wherein each uncharged linkage is a phosphorodiamidate linkage as represented at Figure 2B, where $X=NR_2$, where R is hydrogen or methyl, $Y=O$, and $Z=O$.

22. The method of claim 21, wherein each linkage is a phosphorodiamidate linkage as represented at Figure 2B, where $X=NR_2$, where R is hydrogen or methyl, $Y=O$, and $Z=O$.

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23. The method of claim 17, wherein the antisense oligomer has a length of from 15 to 20 subunits.

24. The method of claim 17, wherein the target sequence is a translation initiation region in an mRNA transcribed from a gene selected from the group consisting of *zipA*, *sulA*, *secA*, *dicA*, *dicB*, *dicC*, *dicF*, *ftsA*, *ftsI*, *ftsN*, *ftsK*, *ftsL*, *ftsQ*, *ftsW*, *ftsZ*, *murC*, *murD*, *murE*, *murF*, *murG*, *minC*, *minD*, *minE*, *mraY*, *mraW*, *mraZ*, *seqA* and *ddlB*.

25. The method of claim 24, wherein the target sequence is a translation initiation region in an mRNA transcribed from a *dic* gene selected from the group consisting of *dicA*, *dicB*, *dicC* and *dicF*.

26. The method of claim 25, wherein the targeting sequence has a sequence selected from the group consisting of SEQ ID NO:45 (*E. coli dicF*), SEQ ID NO:48 (*E. coli dicA*), SEQ ID NO:49 (*E. coli dicB*), SEQ ID NO:50 (*E. coli dicC*); and SEQ ID NO:61 (*S. typhi. dicA*).

27. The method of claim 26, wherein the targeting sequence has the sequence presented as SEQ ID NO:45.

28. The method of claim 27, wherein the antisense oligomer is a morpholino oligomer.

29. The method of claim 24, wherein the targeting sequence is complementary to a translation initiation region in an mRNA transcribed from a *secA* gene, and has a sequence selected from the group consisting of SEQ ID NO:47 (*E. coli secA*), SEQ ID NO:67 (*Staph. aureus secA*), SEQ ID NO:79 (*H. pylori secA*), and SEQ ID NO:91 (*Treponema pallidum secA*).

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30. The method of claim 29, wherein the targeting sequence has the sequence presented as SEQ ID NO: 47.

31. The method of claim 30, wherein the oligomer is a morpholino oligomer.

32. The method of claim 18, wherein the targeting sequence has a sequence selected from the group consisting of SEQ ID NO: 103 (*E. faecium* carbamate kinase); SEQ ID NO: 104 (*E. faecium* D-ala D-ala ligase); SEQ ID NO: 105 (*E. faecalis* topoisomerase); SEQ ID NO: 107 (*E. faecalis repA*); SEQ ID NO: 108 (*E. faecalis* alkyl hydrogen peroxide reductase); SEQ ID NO: 109 (*E. faecalis* thioredoxin reductase); SEQ ID NO: 110 (*E. faecalis* dihydrofolate reductase); SEQ ID NO: 111 (*E. faecalis ftsA*); and SEQ ID NO: 112 (*E. faecalis* cell wall enzyme).

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33. The method of claim 32, wherein the oligomer is a morpholino oligomer.

34. The method of claim 17, for treating bacterial infections of the skin, wherein said administering is by a topical route.

35. The method of claim 17, for use in treating a bacterial respiratory infection, wherein said administering is by inhalation.

36. A livestock and poultry food composition containing a food grain supplemented with a subtherapeutic amount of an antibacterial compound, said compound consisting of a substantially uncharged antisense oligomer containing from 8 to 40 nucleotide subunits, including a targeting nucleic acid sequence at least 10 nucleotides in length which is effective to hybridize to (i) a bacterial tRNA or (ii) a target sequence, containing a translational start codon, within a bacterial nucleic acid which encodes a protein associated with cell division or cell wall synthesis,

said protein being selected from the group consisting of *zipA*, *sulA*, *secA*, *dicA*, *dicB*, *dicC*, *dicF*, *ftsA*, *ftsI*, *ftsN*, *ftsK*, *ftsL*, *ftsQ*, *ftsW*, *ftsZ*, *murC*, *murD*, *murE*, *murF*, *murG*, *minC*, *minD*, *minE*, *mraY*, *mraW*, *mraZ*, *seqA*, and *ddlB* proteins, carbamate kinase, D-ala D-ala ligase, topoisomerase, alkyl hydroperoxide reductase, thioredoxin reductase, dihydrofolate reductase, and cell wall enzyme;

wherein: each of said subunits comprises a 5- or 6-membered ring supporting a base-pairing moiety effective to bind by Watson-Crick base pairing to a respective nucleotide base in the bacterial nucleic acid sequence,

adjacent subunits are joined by uncharged linkages selected from the group consisting of: uncharged phosphoramidate, phosphorodiamidate, carbonate, carbamate, amide, phosphotriester, alkyl phosphonate, siloxane, sulfone, sulfonamide, sulfamate, thioformacetyl, and methylene-N-methylhydroxylamino, or by charged linkages selected from the group consisting of phosphate, charged phosphoramidate and phosphorothioate,

and the ratio of uncharged linkages to charged linkages in the oligomer is at least 4:1.

37. The composition of claim 36, wherein the oligomer is a morpholino oligomer.

38. The composition of claim 37, wherein each linkage is a phosphorodiamidate linkage as represented at Figure 2B, where $X=NR_2$, where R is hydrogen or methyl, $Y=O$, and $Z=O$.

39. The composition of claim 36, wherein the antisense oligomer has a length of from 15 to 20 nucleotide subunits.

40. A method of preparing a vaccine against a selected bacteria, comprising:

incubating the bacteria in the presence of an antisense morpholino-based antisense oligomer having

(a) from 8 to 40 nucleotide subunits, including a targeting base sequence effective to hybridize to a translation initiation region in an mRNA transcribed from a gene of the selected bacteria, selected from the group consisting of *zipA*, *sulA*, *secA*, *dicA*, *dicB*, *dicC*, *dicF*, *ftsA*, *ftsI*, *ftsN*, *ftsK*, *ftsL*, *ftsQ*, *ftsW*, *ftsZ*, *murC*, *murD*, *murE*, *murF*, *murG*, *minC*, *minD*, *minE*, *mraY*, *mraW*, *mraZ*, *seqA* and *ddlB*; and

(b) uncharged phosphorous-containing intersubunit linkages, as shown in Figures 2A-2D herein;

in an amount of oligomer effective to produce replication-crippled, morphologically abnormal bacterial cells.

41. A method of vaccinating a human or animal subject against a selected bacteria, comprising:

administering to the subject, replication-crippled, morphologically abnormal cells of the bacteria, prepared by incubating the bacteria in the presence of a morpholino-based antisense oligomer having

(a) from 8 to 40 nucleotide subunits, including a targeting base sequence effective to hybridize to a translation initiation region in an mRNA transcribed from a gene of the selected bacteria, selected from the group consisting of *zipA*, *sulA*, *secA*, *dicA*, *dicB*, *dicC*, *dicF*, *ftsA*, *ftsI*, *ftsN*, *ftsK*, *ftsL*, *ftsQ*, *ftsW*, *ftsZ*, *murC*, *murD*, *murE*, *murF*, *murG*, *minC*, *minD*, *minE*, *mraY*, *mraW*, *mraZ*, *seqA* and *ddlB*; and

(b) uncharged phosphorous-containing chiral intersubunit linkages, as shown in Figures 2A-2D herein.